BIOTEMAS, 1(2): 1-40, 1988

REVIEW

EXCITATORY AMINO ACID NEUROTRANSMISSION IN THE CEREBRAL CORTEX

J.I. Addae[1] and T.W. Stone[2]

[1] *Department of Physiology, University of West Indies, Eric Williams Medical Complex, Uriah Butler Highway, Champs Fleurs, Trinidad and Tobago*

[2] *Department of Physiology, St George's Hospital Medical School, London SW17 ORE - UK*

Correspondence: Dr. J.I. Addae, address above.

Key words: Excitatory amino acids, Glutamate, Aspartate, Quinolinic acid, Kynurenic acid, Cerebral cortex and Desensitisation.

1.0 INTRODUCTION

The excitatory amino acids (EAAs) have come to be accepted as probably involved in the normal and abnormal function of the central nervous system. Since Curtis, Phillis and Watkins (1959, 1960) began a systematic study of the actions of EAAs in central neurones several research workers have become involved in extensive multidisciplinary studies to elucidate the precise roles and mechanisms of action of these EAAs and their antagonists (for previous reviews see Watkins and Evans, 1981; McLennan, 1983; Fonnum, 1984; Foster and Fagg, 1984; Stone and Burton, 1988). Electrophysiological and bio-

chemical experiments using conformationally restricted agonists in the vertebrate CNS has led to the characterisation of EAA receptors into three pharmacologically distinct types (McLennan and Lodge, 1979; Watkins and Evans, 1981; McLennan 1983; Davies et al., 1983; Watkins, 1984). Although there have been different modifications to this classification to give a fourth receptor type (Luini et al., 1981; Fagni et al., 1983; Foster and Fagg, 1984) the present consensus seems to settle on the three-receptor classification. This classification consists of:

(1) N-methyl-D-aspartate (NMDA) receptor site

(a) acted on by NMDA, NMLA, homocysteic acid and quinolinic acid.

(b) blocked by:

(i) D(-)-2-amino-5-phosphonopentanoic acid (AP5 or APV), D(-)-2 amino-7 phosphonoheptanoic acid (AP7 or APH) [Davies et al., 1981b; Perkins et al., 1981; Stone et al., 1981; Evans and Watkins, 1981].

(ii) the dissociative anaesthetic ketamine (Anis et al., 1982; Lodge and Johnston, 1985; Harrison and Simmonds, 1985), phencyclidine and the sigma opiate cyclazocine (Lodge and Anis, 1982; Thomson and Lodge, 1985).

(iii) MK-801 [(+)-5-Methyl-10,11-dihydro-5H-dibenzo [a,d] cyclo-hepten-5,10-imine maleate] (Drejer and Honoré, 1987; Wong et al., 1986; Woodruff et al., 1987)

(iv) CPP [3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid] (Davies et al., 1986).

(v) D-α-aminoadipate (DαAA) [Hall et al., 1977; Biscoe et al. 1977; Davies and Watkins, 1979].

(vi) Mg^{++}, Zn^{++} and other metal ions (Davies and Watkins, 1977; Evans et al., 1977; Coan and Collingridge, 1985, Peters et al., 1986; Westbrook and Mayer, 1987.

(2) Quisqualate receptor site

(a) activated selectively by quisqualic acid (from the plant Quisqualis) and (+)-2-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA).

(b) blocked by:

(i) γ-D-glutamylaminomethylsulphonate (GAMS) [Davies et al., 1983; Davies and Watkins, 1985].

(ii) γ-D-glutamyltaurine (γ-D-glu-tau) [Davies et al., 1983].

(iii) Pentobarbital (Teichberg et al., 1984; Harrison, 1985; Sawada and Yamamoto, 1985; Addae and Stone, 1987).

(3) Kainate receptor site

(a) activated selectively by kainic and domoic acids (from the marine algae Digenea simplex and Chondria armata respectively).

(b) blocked by GAMS and γ-D-glu-tau (Davies et al., 1983).

Whereas the antagonists to NMDA are selective and potent GAMS and γ-D-glu-tau are not as potent for the kainate and quisqualate receptors and do antagonise NMDA to some extent (Davies et al., 1983). The availability of selective NMDA antagonists has led to better characterisation and understanding of the NMDA receptor. Other established EAA antagonists include kynurenic acid (an endogenous metabolite of tryptophan [Perkins and Stone, 1982; Ganong et al., 1983; Herrling, 1985], (+ cis-2,3-piperidine dicarboxylic acid (cis PDA) [Davies et al., 1981a; Surtees and Collins, 1985) and γ-D-glutamyl glycine (DGG) [Francis et al., 1980; Davies et al., 1983; Surtees and Collins, 1985]. These antagonists, however, exhibit poor selectivity between the three types of EAA receptors. L-glutamic acid diethyl ester (GDEE) was initially reported to be a selective quisqualate antagonist (McLennan and Lodge, 1979; Davies and Watkins, 1979; however both its EAA antagonism and its selectivity have not been consistently observed (Spencer et

al., 1976; Luini et al., 1981).

The endogenous EAAs L-glu and L-asp activate all the three types of receptors and are therefore regarded as mixed agonists (Watkins and Evans, 1981). L-asp had been thought of as producing its effect mainly via the NMDA receptor whereas L-glu was considered to activate primarily the quisqualate receptor (Watkins and Evans,1981). Among the endogenous EAAs, however, L-glu has the highest affinity for the APV (which labels the NMDA) binding sites (Olverman et al., 1984). Intracellular recordings from neocortical slices indicate that the actions of NMDA are best mimicked by the endogenous EAA L- homocysteic acid and not by L-glu. (Knopfel et al, 1987). Nevertheless, L-glu continues to enjoy the prime position as the most favoured transmitter at all three EAA receptor sites.

1.1. MECHANISM OF ACTION OF EXCITATORY AMINO ACIDS (EAAs)

The early experiments using intracellular recordings indicated that an EAA produced membrane depolarisation which if of sufficient magnitude initiated a spike potential (Curtis, Phillis and Watkins, 1959; 1960; Bradford and McIlwain, 1966). The conductance mechanism underlying the depolarisation was, however, more difficult to determine. The EAA receptors seemed to be linked to different conductance mechanisms. NMDA and L-asp responses are now known to be generated by a voltage-dependent conductance, exhibiting a negative-slope conductance at membrane potentials more negative than -30mV. The conductance mechanisms linked to the kainate and quisqualate receptors are less sensitive to the membrane potential (MCDonald and Wojtowicz, 1982; MacDonald and Porietis, 1982; Mayer and Westbrook, 1984). The mixed agonist nature of L-glu could account for the earlier findings that it increased, decreased or failed to alter the membrane conductance (Engberg et al., 1978; Engberg, Flatman and Lambert, 1979; Hablitz and Langmoen, 1982).

Voltage-and patch-clamp studies in cultured cells and neocortical slices have shown that Mg^{++} ions block the ionic channels associated with the NMDA receptor in a voltage-dependent manner i.e. Mg^{++} exerts increasingly powerful block at more negative membrane potentials. This effect of Mg^{++} can fully account for the voltage-dependency of the NMDA-evoked conductance (Nowak et al., 1984; Mayer and Westbrook, 1984, 1985; Thomson, 1986). Current-voltage plots from volta-

ge- and patch-clamp studies suggest that all the three selective agonists act by activating non-selective cationic channels (Nowak and Asher, 1984; Mayer and Westbrook, 1985).

Activation of the NMDA receptor has been shown to cause opening of Ca^{++} channels in cultured spinal neurones; these channels being different from the voltage-gated Ca^{++} channels (Mayer et al., 1987).The non-NMDA agonists did not appear to open ligand-gated Ca^{++} channels in the spinal neurones. However, kainate and quisqualate have been found to open ligand-gated channels in cultured striatal neurones (Murphy et al., 1987). There is no obvious reason to account for the discrepancy except that it may be due to regional differences in the source of the cultured neurones.

Besides the Mg^{++} -sensitive site the NMDA receptor-channel complex appears to have other regulatory units. Glycine potentiated the effect of NMDA on channel openings in a patch-clamp study on cultured cortical neurones (Johnson and Ascher, 1987). Glycine also incresead the effect of NMA (racemic N-methyl-aspartate)on the binding of the labelled phencyclidine analogue TCP ([3H]N-(1-[-thienyl] cyclohexyl piperidine) to hippocampal membranes (Bonhaus et al., 1987). These results suggested that glycine may regulate the activity of the NMDA receptor-channel complex by acting at a strychnine-insensitive allosteric site. The psychomimetic drug phencyclidine ("angel dust") is suspected to act at a site near to or within the NMDA activated ionic channel (Honey et al., 1985; Javitt et al., 1987, Wroblewski et al., 1987). Zukin et al. (1987) have identified an endogenous ligand for the phencyclidine receptor from bovine hippocampal extract. It remains to be determined whether the endogenous ligand has a physiological action on the NMDA receptor-channel complex.

1.2 EFFECTS OF EAAs ON SECONDARY MESSENGERS

The EAAs cause dose-dependent increases in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) syntheses in central neurones (Shimizu et al., 1974; Kinscherf et al.,1976; Novelli and Henneberry, 1985) in a Ca^{++}-dependent manner (Ferrendelli et al., 1974). Other depolarising agents such as high K^{+}, ouabain and veratridine similarly increases cGMP levels (Kinscherf et al., 1976; Novelli and Henneberry, 1985). It has been suggested that the effects of EAA could be secondary to the depolarisation and subsequent Ca^{++}

influx (Watkins and Evans, 1981). However, imipramine effectively blocks the veratridine-evoked accumulation of cGMP without much action on the effect of glu , suggesting that veratridine and glu may be causing cGMP accumulation via different mechanisms (Novelli and Henneberry, 1985).

Studies on the effect of EAAs on phosphatidyl inositol (PI) metabolism are still in their early stages. The emerging pattern is that quisqualate significantly increases PI metabolism whereas NMDA and kainate have only weak effects (Nicoletti et al., 1986b., Baudry et al., 1986, Récasens et al., 1987; Schmidt et al., 1987). However, NMDA and kainate can potently inhibit carbachol-induced stimulation of PI metabolism (Baudry et al, 1986; Schmidt et al, 1987). The EAA-induced increase in PI metabolism, particulary that caused by quisqualate, is highest in foetal and neonatal brains and declines with age (Nicolletti et al., 1986a., Slacdec zek et al., 1986; Récasens et al., 1987) and may play a role in synaptogenesis (Récasens et al.,1987) Intracellular injection of the active protein kinase C into hippocampal CA1 neurones evoked features of long term potentiation (Hu et al., 1987). However, the LTP induced via the NMDA receptor does not appear likely to be mediated by protein kinase C because of the weak effect of NMDA on PI metabolism. It appears, nevertheless, that there may be a possible involvement of PI metabolism in mediating use-dependent changes at glutamatergic synapses.

1.3 MECHANISM OF ACTION OF ANTAGONISTS

The actions of the NMDA antagonists APV, APH, CPP and D∝AA appear to be competitive (Evans et al., 1979; Harrison and Simmonds, 1985; Leach et al., 1986; Wheatly and Collins, 1986). Similarly, kynurenic acid has been shown to block both the NMDA and non-NMDA receptors in a competitive manner (Herrling, 1985).

In contrast, the antagonism of NMDA by Mg^{++} shows non-competitive kinetics (Harrison and Simmonds, 1985; Mayer and Westbrook, 1985) which together with the voltage-dependency of the Mg^{++} block suggests that Mg^{++} enters and blocks the channel linked to the NMDA receptor (Mayer and Westbrook, 1985; Nowak et al., 1984).

Ketamine, phencyclidine and MK-801 also block NMDA in a non-competitive manner but seem to act at sites different from where Mg^{++} acts (Harrison and Simmonds, 1985; Martin and Lodge, 1985; Lodge and

Johnston, 1985; Javitt et al., 1987; Woodruff et al., 1987). The voltage-dependent actions of ketamine and phencyclidine suggest, like Mg^{++}, they may act at a site within the NMDA-activated channel (Honey et al., 1985; MacDonald et al., 1987).

1.4 SYNTHESIS, RELEASE AND INACTIVATION OF GLUTAMATE

The level of glutamate in neurones and glia does not appear to be significantly influenced by the blood glu levels (Oldendorf, 1971; Oldendorf and Szabo, 1976). The two main precursors for the synthesis of the transmitter (releasable) pool of glutamate are glucose (Potashner, 1978; Bradford et al., 1978; Hamberger et al., 1979) and acetate (Berl et al., 1961; Michin and Fonnum, 1979). Glucose is metabolised to α-ketoglutarate (αKG) in the nerve terminal via the Krebs cycle. αKG can also be synthesised in the astroglial cells via pyruvate carboxylase and then transported into the nerve terminals (Shank and Campbell, 1982; Shank et al., 1985) where it is transaminated to glu by aspartate aminotransferase or ornithine aminotransferase.

Acetate is mainly converted in astroglial cells to glutamine. A proportion of the synaptically released glu is taken up by astroglia and converted to glutamine by glutamine synthetase. Glutamine is transported from astroglia into the nerve terminals and converted to glu by phosphate activated glutaminase (Bradford and Ward, 1976; Weiler et al., 1979).

Naito and Ueda (1983, 1985) have demonstrated an uptake of glu into synapsin I-associated synaptic vesicles; the uptake being driven by an electrochemical proton gradient generated by Mg-ATPase. Nicholls and Sihra (1986) have also demonstrated the release of endogenous glu from a non-cytoplasmic pool in synaptosomes. As with the other neurotransmitters such as acetylcholine and aminobutyric acid the release of glu from presynaptic nerve terminals is initiated by an increase in the cytosolic concentration of Ca^{++} in the terminals (Bradford et al., 1973; Pastuszko et al., 1984; Bradford et al., 1986; Nicholls and Sihra, 1986). An additional means by which neurones may release glu is possibly from the cytosolic pool by a reversal of the glu uptake system (see Erecinska, 1987).

The major means through which the action of synaptically released glu is terminated has been established to be through re-uptake by neuronal and glial cells via both high and low affinity uptake sys-

tems (Logan and Snyder, 1971; Schousboe et al., 1977; Weiler et al., 1979; Vincent and McGeer, 1980). The high affinity uptake system (apparent Km<50 μM) is widely distributed in the CNS and acts on mainly L-glu, L-asp and D-asp (Logan and Snyder, 1971; Benjamin and Quastel, 1976; Davies and Johnston, 1976). The low affinity uptake system (apparent Km>100 μM) is present throughout the CNS and affects not only L-glu and L-asp but also non-transmitter EAAs such as D-asp, D-glu (Benjamin and Quastel, 1976) and quisqualate (Lodge et al., 1980).

The uptake of glu involves a co-transport of two sodium ions with one glu (or asp) molecule (Wheeler and Hollingsworth, 1978, Stallcup et al., 1979, Erecińska et al., 1986). The uptake is driven by a combination of the transmembrane potential and Na^+ concentration gradient (Erecińska et al., 1986, Erecińska, 1987, Wheeler, 1987). Based on kinetic studies using cortical membranes Wheeler (1987) has proposed that there is only one glutamic acid carrier the properties of which can account for the previously accepted low and high affinity systems. It remains to be established whether the same or similar carrier participates in the uptake of glu by glia, or the uptake of other endogenous EAAs by neurones and glia.

2.0 EVIDENCE FOR NEUROTRANSMITTER ACTION OF L-GLUTAMATE IN THE CEREBRAL CORTEX

The endogenous EAAs (e.g. L-glu, L-asp, L-cysteate, L-homocysteate and quinolinate) were easily established as depolarising agents in the cerebral cortex and other parts of the CNS (e.g. Curtis et al., 1959, 1960; Stone and Burton, 1988). However, a neurotransmitter role for any of these EAAs in the cerebral cortex has been difficult to establish unequivocally. There are a number of criteria that are important for the identification of a synaptic transmitter (Werman, 1966; Orrego, 1979; Watkins and Evans, 1981). These are:

(1) The transmitter candidate must be shown to be present in the pre-synaptic nerve and released from the nerve terminals by appropriate stimulation.

(2) When exogenously applied, the transmitter candidate must have a post-synaptic action identical to that of the synaptically released substance, including antagonism by specific pharmacological compounds.

(3) There must be a mechanism for inactivating the transmitter once it has been released into the synaptic cleft. This criterion has been conclusively established for L-glu as discussed.

In the cerebral cortex because of the paucity of well defined tracts which are amenable to selective experimentation the first, or "release", criterion has been difficult to satisfy.

Nevertheless, there have been examples of Ca^{++} -dependent release of L-glu from both *in vivo* and *in vitro* experiments. Glu was selectively released from the cortical surface during desynchronising stimulation of the mid-brain reticular formation to simulate an "arousal" cortical response (Jasper and Koyama, 1969). Glu was also selectively released from the sensorimotor cortex by stimulation of the contralateral, but not the ipsilateral, brachial plexus (Abdul-Ghani *et al.*, 1979). There was release of glu from the visual cortex following direct electrical stimulation or application of KCl solution (Clarke and Collins, 1976). Collins (1970) demonstrated the release of glu and asp from the olfactory cortical slice by electrical stimulation of the lateral olfactory tract or activation of the deep and superficial pyramidal cells. Release of glu has also been reported from slices of the visual cortex (Baughman and Gilbert, 1981). Hemidecortication led to a decrease in the endogenously released glu from the parietal cortex of freely moving rats suggesting that glu could be a transmitter at the terminals of some transcallosal fibres (Peinado *et al.*, 1987). The released glu, however, could have come from either the neuronal or astroglial cells (Mitchell, 1975; Clarke and Collins, 1976). Although circumstantial evidence of a Ca^{++}-dependent release of glu by glia has been reported (Roberts, 1974b), neuronal glu release has generally been distinguished from glial release by the Ca^{++} -dependency of the former (e.g. Orrego, 1979, Sanchez-Preto *et al.*, 1987.).

The second, or "identity of action" criterion is best studied using intracellular recording from a post-synaptic cell to enable one to measure changes in more precise biophysical parameters e.g. membrane potential and resistance, and ionic equilibrium potential (Werman, 1966). Kynurenic acid and D-glutamylglycine have been shown to decrease the spontaneous and evoked epsps as well as responses to iontophoretic NMDA, quisqualate and kainate in dissociated cultures of neurones from rat visual cortex (Huettner and Baughman, 1985).

Using rat neocortical slices, Thomson (1986) has described an

atypical epsp which had similar properties to the membrane changes evoked by iontophoretic NMA. This epsp and a component of the more conventional epsp were blocked by APV, ketamine and cyclazocine (Thomson, 1986; Thomson, West and Lodge, 1985). Intracellular recordings from slices of the rat visual cortex coupled with high frequency stimulation of the optic radiation showed induction of long term potentiation which was blocked by APV (Artola and Singer, 1987).Similarly, thalamic stimulation applied as a train of 10-15 pulses at 10Hz induced augmenting response in the rat sensorimotor cortex, the response being blocked by topically applied APV (Addae and Stone,1987).Kleinschmidt, Bear and Singer (1987) have demonstrated that APV disrupts the experience-dependent plasticity in the kitten striate cortex. The receptor specificity of APV implies the presence of functional NMDA receptors in these neocortical areas.

Due to the technical difficulties associated with intracellular recording from the cortex in vivo, experiments to satisfy the identity of action criterion in such systems have involved mainly extracellular recordings. APV, D- -aminoadipate and kynurenic acid blocked the synaptic activity following photic and cortical stimulation as well as responses to iontophoretic asp and glu in the visual cortex (Hicks et al., 1981; Hicks and Guedes, 1983; Tsumoto et al., 1986).

A number of reports have favoured glu (or asp) as the transmitter used by corticofugal fibres e.g. cortico-cuneate (Stone,1976), and corticostriatal pathways (Stone, 1979; Herrling, 1985). The pyramidal cells which give rise to these cortico-fugal fibres also have recurrent collaterals which synapse within the cerebral cortex. Since a matured neurone probably releases the same transmitter (or combination of transmitters) at all its nerve endings (ammended Dale's principle) the above findings would seem to provide circumstantial evidence that glu (and asp) could be synaptically released in the cerebral cortex.

Studies involving retrograde transport of the metabolically stable D-[3H]-aspartate has led to the suggestion that the thalamo-cortical pathways may be using glu and asp at the nerve terminals in the visual (Baughman and Gilbert, 1981) and sensorimotor cortices (Ottersen et al., 1983). Glu has been localised in the cerebral cortex of rats and monkeys using immunocytochemical techniques (Conti et al., 1987). The latter study demonstrated a laminar distribution of the

immunostained glu-containing neurones with laminae II, III, V, and VI exhibiting the highest densities. The method, however, is unable to distinguish between the glu present in the metabolic pool from that within the transmitter pool.

Although the demonstration of binding sites in a tissue does not necessarily make the endogenous ligand a transmitter a conclusive demonstration of binding sites on postsynaptic membranes strengthens the case for a transmitter role for the compound in question. Roberts (1974a) was the first to report specific binding of labelled glu to neocortical membranes. Since then there have been several studies to demonstrate specific sodium-independent binding of glu to cortical membranes (e.g. De Robertis and De Plazas, 1976; Sanderson and Murphy, 1982); sodium-dependent binding is considered to reflect binding to the glu uptake sites. Few studies have however used membrane fractions consisting of postsynaptic membranes. Thus extrasynaptic location of the binding sites cannot be excluded. Fagg and Matus (1984) have demonstrated L-glu binding sites on rat brain post-synaptic densities (PSDs). Histologically the PSDs looked like post-synaptic membranes. Wu et al. (1986) have similarly demonstrated binding of L-glu to the PSD fraction from canine cerebral cortex.

The usual ligand binding experiments suffer from the mixing together of broken membranes from different cell types.

Receptor autoradiography can offset this limitation by demonstrating the location of receptors on the intact cell (Snodgrass,1975). In the cerebral cortex quantitative autoradiography has been useful in determining the distribution of the binding sites for the selective EAA agonists (Unnerstal and Wamsley, 1983; Monaghan and Cotman, 1982, Monaghan et al., 1984a, 1984b, and 1985; Greenamyre et al.,1985a., Maragos et al., 1986). These studies indicate that the quisqualate and NMDA binding sites are concentrated in the superficial cortical layers (I, II, III) whereas kainate binding sites are mostly located in the deeper layers (V, VI).

When taken together, the above results which have emanated from different experimental approaches appear to provide the cardinal and supportive evidence necessary to justify the consideration of glu as a major excitatory neurotransmitter in the mammalian cerebral cortex.

3.0 LOSS OF CORTICAL RESPONSE TO EXCITATORY AMINO ACIDS

Prolonged or repeated application of some EAAs to the cerebral cortex leads to a loss of the cortical response to the EAAs (Addae and Stone, 1986; 1987). Such an observation could have been due to a non-specific loss of neuronal excitability following excessive depolarisation, or secondary to specific EAA receptor-mediated desensitisation. The first mechanism tends to cause non-selective loss of sensitivity to all excitatory compounds whilst desensitisation is likely to be restricted to a group pf compounds. Desensitisation may involve a change in the conformation of the receptor to an inactive state (Katz and Thesleff, 1957) or inactivation of the ionic channel or the transductive (second messenger) system.

(Nastuk and Parsons, 1970). In recent years several studies have demonstrateo loss of response to prolonged or repeated application of EAAs to neurones from different areas of the nervous system. Table I summarises some of the reports. The results of these experiments, particularly those involving patch clamping of cultured neurones,provide convincing evidence to support desensitisation of the receptor complex to some of the EAAs.

Whereas loss of response to agonists acting on the NMDA and quisqualate receptores have been consistently shown, loss of response to kainate *in vivo* has not been easy to demonstrate (Addae and Stone, 1987). Indeed, a number of *in vitro* studies have suggested that there is no appreciabe desensitisation to kainate (Fagni *et al.*, 1983b; Mayer and Westbrook, 1985; Vyklický *et al.*, 1986; Vlachová *et al.*, 1987).

3.1 INTERACTIONS BETWEEN EXCITATORY AMINO ACIDS

When a cell or tissue is exposed to a compound it may exhibit desensitisation to only that compound (homologous desensitisation) or to other compounds acting on different receptors as well (heterologous desensitisation). The latter situation usually implies that the mechanism of desensitisation occurs downstream to the ligand binding site; whilst homologous desensitisation suggests the process is restricted to the receptor itself. Heterologous desensitisation further suggests that the compounds involved share some common pathway following activation of their receptors (Triggle, 1981; Hertel and Perkins, 1984). Although quisqualate, NMDA and kainate are supposed to act on different receptors (McLennan and Lodge, 1979; Watkins and Evans, 1981) when applied to the somatosensory cortex NMA prevented the action of kainate in altering the somatosensory evoked potentials; and quisqualate prevented the effects of NMA and kainate(Addae and Stone, 1987). Similarly in the horizontal cells of vertebrate retina NMA inhibited responses to kainate (Bloomfield and Dowling,1985; Cunningham and Neal, 1985) and quisqualate suppressed response to kainate (Ishida and Neyton, 1985). Voltage-clamp studies with dissociated hippocampal neurones have also shown quisqualate-induced desensitisation to kainate (Kiskin et al., 1986). These reports of cross-desensitisation between the EAAs indicate that the site of EAA-induced desensitisation is likely to be distal to the agonist binding site.

3.2 MECHANISM OF DESENSITATION TO EXCITATORY AMINO ACIDS

Few reports have attempted to elucidate the mechanisms underlying desensitisation to EAAs. Fagni et al. (1984) found that there was no change in the resting membrane potential or input resistance during the period of desensitisation to NMA and L-glutamate. Desensitisation to EAAs has been reported to be enhanced by increasing extracellular Ca^{++} concentration and inhibited by Ca channel blockers such as cobalt and verapamil (Zorumski and Fischbach, 1985; Murali Mohan and Sastry, 1986). Mayer and Westbrook (1985) also observed an association between the desensitisation to NMDA and activation of voltage-sensitive calcium channels. Thus calcium influx appears to link the activation of the EAA receptor and initiation of the desensitising process. A similar involvement of Ca^{++} has been observed in

TABLE I

A summary of studies in which central neurones have been reported to exhibit desensitisation to excitatory amino acids

Types of neurones studied	Experimental method	Excitatory amino acids to which desensitisation was observed	Reference
Hippocampal slices	Extracellular recordings from CAI cells	L- and D-glu; L-asp; L-cysteine sulfinate; NMA	Fagni et al., 1983a and 1983b
Striatal slices	Evoked release of [^{3}H]ACh	NMDA, quinolinate	Lehman et al., 1985
Hippocampal slices	Intracellular recordings from CAI	L-glu	Bernstein and Fischer, 1985
Cultured cerebellar neurones	Patch clamp	L-glu	Cull-Candy and Ogden, 1985
Medial vestibular nuclear slices	Intracellular recordings	NMDA, quisqualate	Lewis et al., 1985
Cultured spinal neurones neurones	Voltage clamp	NMDA	Mayer and Westbrook, 1985
Hippocampal slices	Extracellular recordings from CAI cells	NMDA, L-glu	Murali, Mohan and Sastry, 1985

Type of neurone	Method	EAAs	Reference
Neocortical neurones (*in vivo*)	Extracellular recordings; Evoked potentials and single cell activity	L-glu, NMA, DLH, quinolínate, quisqualate	Addae and Stone, 1986 and 1987
Olfactory cortical slices	Extracellular recordings; evoked potentials	L-glu, L-asp	Braitman, 1986
Dissociated hippocampal pyramidal cells	Voltage clamp	L-glu, quisqualate	Kiskin *et al.*, 1986
Cultured chick spinal cord	Patch clamp	NMDA, quisqualate, glu, asp	Vyklický *et al.*, 1986 Vlachová *et al.*, 1987
Dissociated chick cord neurones	Patch clamp	NMDA, L-glu	Zorumski and Fischbach, 1985

the desensitisation to other compounds such as acetylcholine(Manthey, 1966; Nastuk and parsons, 1970) and GABA (Sarne, 1976).

Intracellular accumulation of Na^+ during application of EAAs has been suggested by Collins and Surtees (1986) to underlie the loss of sensitivity to EAAs in the olfactory cortical slice. Since increasing the intracellular Na^+ could cause a secondary increase in the intracellular Ca^{++} by inhibiting the sodium-calcium exchanger, there could be a link between these two proposed mechanisms. This link is supported by the observation that other procedures which increase the intracellular Ca^{++} concentration such as Mg^{++} -free bathing solutions (by increasing Ca^{++} influx) or low Na^+ solutions (by inhibiting the Na^+/Ca^{++} exchanger) tend to enhance desensitisation to NMDA in cultured spinal neurones (Mayer and Westbrook, 1985).

Watkins (1984) has hypothesized that the influx of Ca^{++} accompanying NMDA receptor activation (Dingledine, 1983; Mayer et al.,1987), could induce efflux of Mg^{++} which would then block the NMDA effects (Davies and Watkins, 1977; Evans et al., 1977; Coan and Collingridge, 1985) thus producing a negative feedback effect to reduce NMDA actions. Whereas such a mechanism could account for the desensitisation to NMDA it cannot apply to desensitisation to quisqualate since the effects of quisqualate are not blocked by Mg^{++} (Mayer and Westbrook, 1984; Nowak et al., 1984).

The observation of cross desensitisation between the EAAs has raised the possibility that the various EAAs could be acting on the same receptor (Kiskin et al., 1986). A ligand binding study has pointed to the possibility that the NMDA receptor could be a manifestation of the quisqualate receptor in a low affinity state (Greenamyre et al., 1985).

Evidence from whole cell and outside out patch clamp studies with cultured cerebellar (Cull-Candy and Ogden, 1985; Cull-Candy and Usowicz, 1986) and hippocampal neurones (Jahr and Stevens, 1986) have indicated that the EAA receptor complex can exist in three or more conductance substates. Kainate or quisqualate activate a small conductance channel (approximately 2pS and 0.5ms duration) whereas NMDA activates a large conductance channel (approximately 50pS and 5ms duration). These results would seem to support a model in which inactivation of the EAA receptor complex by one selective agonist would render the receptor complex unresponsive to other selective agonists - a

situation which would manifest an heterologous desensitisation between the EAAs in some of the experimental systems. Such a model maintains that there are separate receptor sites for the selective EAA agonists and that desensitisation to the EAAs occur at the channel level.

From our observations and those from in vitro studies (Addae and Stone, 1986, 1987; Fagni et al., 1983b; Kiskin et al., 1986; Vyklický et al., 1986; Vlachová et al., 1987) the tendency for the EAAs to induce desensitisation would seem to be of the order of quisqualate>NMDA>>kainate. The question that needs to be addressed is why there is such a marked difference in the desensitising capabilities of quisqualate and kainate in spite of their ability to activate similar (or the same) ionic channels. A proper resolution of this question will depend on the development of more specific pharmacological and biophysical probes to characterize the receptor sites and the ionic channels linked to them.

Because quisqualate activates phosphatidyl inositol (PI) metabolism to a much greater extent than kainate (Nicoletti et al.,1986b; Baudry et al., 1986; Récasens et al., 1987) it may be that the inositol triphosphate-induced intracellular release of Ca^{++} enhances desensitisation by quisqualate. Activation of protein kainase C following PI metabolism could possibly lead to inactivation of the EAA receptor complex, in a manner similar to what has been demonstrated for acetylcholine-induced desensitisation (Eusebi et al., 1985; Downing and Role, 1987). It seems possible, however, that desensitisation to EAAs may involve more than one mechanism as has been the case with desensitisation to β-adrenergic agonists (Hertel and Perkins, 1984).

4.0 CLINICAL CORRELATES

Studies on the EAA agonists and antagonists have contributed to the understanding of not only neocortical function but also its dysfunction. This has led to attempts to design novel pharmacological agents to combat some neurological disorders. Localised injection of kainate or the endogenous EAA quinolinate into the brain causes destruction of cell bodies and dendrites without affecting the axons of passage, nerve terminals and glia (Olney, 1971; Coyle and Schwarcz, 1976; Schwarcz et al., 1983; Foster et al., 1983). These changes have been described as similar to the neurodegenerative changes observed

in the striatum in Huntington's disease, (Coyle and Schwarcz, 1976; Olney and de Gubareff, 1978; Beal et al.,1986) and in the hippocampus in temporal lobe epilepsy (Coyle et al., 1981; Schwarcz et al., 1983; Griffiths et al., 1983). The other endogenous EAAs tested - L-asp,homocysteate and cysteine sulphinate - have only weak neurodegenerative properties (Olney and de Gubareff, 1978; Schwarcz et al., 1978) thus leaving quinolinic acid (or another untested endogenous EAA) as the major suspect for the causation of these diseases.

Intracerebral or systemic administration of NMDA, quinolinate, kainate or quisqualate in animals causes generalised epilepsy (Lapin, 1981; Coyle et al., 1981; Czuczwar and Meldrum, 1982; Foster et al., 1983; Fukuda et al., 1985). There is increased release of EAAs associated with neuronal destruction following hypoxia (Rothman, 1984; Hauptman et al., 1984; Hagberg et al., 1987); hypoglycemia (Wieloch et al., 1985) or ischemia (Benveniste et al., 1984; Erecińska et al., 1984; Hauptman et al., 1984; Simon et al., 1984; Drejer et al.,1985). The accumulation of glu probably results from decreased reuptake (Silverstein et al., 1986) following ATP deprivation and inhibition of the Na+/Ka+-pump which controls glu reuptake as well as increased glu release (Dagani and Erecińska, 1987). EAA-induced neurodegeneration in the cortex has been suggested to contribute toward senile dementia (Bowen et al., 1983; Moroni et al., 1984) and Alzheimer's disease (Greenamyre et al., 1985b; Cross et al., 1987). Two excitoxic amino acids β-N-methylamino-L-alanine (BMAA) and β-N-oxalylamino-L-alanine (BOAA), which are present in the edible seeds of Cycas circinalis and Lathyru sativus respectively, have been linked to the pathogenesis of Guam amyotrophic lateral sclerosis and lathyrism (Spencer et al., 1986; Spencer et al., 1987). BMAA and BOAA have been shown to induce neurodegeneration in cortical neurones and to cause convulsions in mice by acting through the NMDA and non-NMDA receptors respectively(Spencer et al., 1987, Ross and Spencer, 1987; Ross et al., 1987).

The toxicity of the EAAs have been regarded mainly to be due to excessive neuronal excitation and depolarisation ("excitotoxicity") which results in excessive Ca^{++} influx (Berdichevsky et al., 1983; Jansco et al., 1984). Ultrastructural studies of gerbil brains following brief ischemia showed accumulation of calcium in the mitochondria of cortical and hippocampal neurones (Dux et al., 1987). The calcium presumably moves into the neurones through glu activation of

ligand-gated channels (Mayer et al., 1987., Murphy et al., 1987) and voltage-gated channels; the former probably being more important (Rothman et al., 1987). In cultured cerebellar neurones the toxicity of kainate was prevented by agents which inhibit the formation of superoxide and hydroxyl radicals (Dykens et al., 1987). The authors have therefore suggested that these radicals may mediate the neuronal damage following Ca^{++} influx. Although this hypothesis is attractive there are a number of missing links which remain to be investigated. The mechanisms of toxicity has alternatively been explained as due to endosmosis resulting from excessive depolarisation and neuronal energy depletion (Coyle et al., 1983) or Cl^- (and Na^+) influx (Rothman, 1984; Olney et al., 1986). Choi (1985) has further suggested that the Cl^- influx is responsible for the acute cellular damage whereas the influx of Ca^{++} accounts for the long term neurotoxicity. EAA antagonists have been used to prevent or minimise the manifestation of EAA-induced toxicity. The antagonists APV and APH have been effective against both EAA-induced seizures (Czuczwar and Meldrum, 1982; Schwarcz et al., 1984) and various animal models of epilepsy e.g. audiogenic seizure in genetically prone DBA/2 mice (Croucher et al., 1982) and seizure in the photosensitive baboon (Meldrum et al.,1983). The neurotoxicity induced by BMMA or BOAA are prevented by APH and cisPDA respectively (Ross and Spencer, 1987; Ross et al., 1987). APH has also been effective in preventing or minimising insulin-induced convulsions (Chapman et al., 1987). APH, APV, γDGG, ketamine and MK-801 have been effective in preventing hypoxic or ischemic neuronal damage (Rothman, 1984; Simon et al., 1984; Rothman et al., 1987a and 1987b; Woodruff, 1987).

In general, the EAA antagonists have the potential of being used in the treatment of some forms of stroke (Schwarcz and Meldrum, 1985; Rothman and Olney, 1986) and neurodegenerative disorders by a direct antagonism of the endogenously released glu or its structural analogue such as quinolinic acid. However, there appear to be serious limitations to their clinical use. The inability of compounds such as APH and APV to cross the blood-brain-barrier implies they can only be administered by the intrathecal route. The non-competitive antagonists ketamine, phencyclidine and MK-801 have the advantage of crossing the blood-brain-barrier and exhibiting use-dependent antagonism at the NMDA receptor (Loo et al., 1986; Fagg, 1987; Woodruff et al., 1987). However, their well known serious psychomimetic effects may limit their clinical use to only life-threatening conditions. The

morphinans - dextrophan and dextromethorphan (present in over-the-counter cough suppressants) - have been shown to be effective in inhibiting the neurotoxic actions of NMDA, quinolinate and glutamate on cultured neocortical neurones (Choi et al., 1987). The clinical safety record of these drugs make them promising candidates for further investigation as to whether they will be devoid of psychomimetic effects at clinically relevant doses. The observation of behavioural disorders (e.g. hyperactivity and ataxia) following the administration of APV, APH and CPP (Koek et al., 1986 ; Compton et al., 1987; O'Neil et al., 1987) could indicate that such psychomimetic side effects may inevitably accompany the use of all NMDA antagonists.

4.1. EFFECTS OF ANTICONVULSANTS ON EXCITATORY AMINO ACIDS

A number of studies have suggested that the clinically used anticonvulsants - pentobarbital, diazepam, diphenylhydantoin, and chlormethiazole - may act by partly antagonising endogenously released EAAs (Weakly, 1969; Richards, 1972; Teichberg et al., 1984; Assumpção et al., 1979; Stone, 1981; Sastry and Phyllis, 1976; Gent and Wacey, 1981). Topical cortical application or systemic administration of pentobarbital and diphenylhydantion indicated that these drugs antagonised glu mainly at the quisqualate receptor site, however, the effective concentrations of both drugs seemed to be higher than the therapeutically relevant levels (Addae and Stone, in press). In the same preparation diazepan appeared to have some inhibitory action on the effect of kainate by a mechanism which did not appear to be via a direct receptor antagonism whilst chlormethiazole and carbamazepine schowed no antagonism to NMA, quisqualate or kainate (Addae and Stone, in press). Using rat cortical slices, Crowder and Bradford (1987) observed that phenobarbital, diphenylhydantoin and carbamazepine inhibited veratridine-stimulated release of endogenous glu and asp at concentrations well above their clinically effective levels. The anticonvulsive effects of these drugs, therefore, do not appear to involve antagonism of an endogenous EAA, at least not in the short term following the administration of the drugs. It remains to be investigated whether the effects of chronic administration of these drugs could involve antagonism of EAAs.

5.0 CONCLUSION

Like the usual desensitisation to other neurotransmitters,hormones or growth factors desensitisation to EAAs seems to be a natural defensive mechanism by neurones against excessive EAA-induced excitation and cell death. Although desensitisation confers an obvious survival advantage on a neurone it could cause certain disadvantages when utilised indiscreetly by the neurones. For example, where repeated transmission via a particular synapse is necessary, the presence of a receptor type which is highly prone to desensitisation could compromise the function of that synapse. Quantitative autoradiographic studies have shown that the quisqualate and NMDA receptors are mainly distributed in the superficial cortical layers whereas the kainate sites are mainly found in the deep layers (Monaghan and Cotman, 1982; Unnerstal and Wamsley, 1983; Monoghan et al., 1984a; 1984b and 1985; Greenmyre et al., 1985a; Maragos et al., 1986). The differences in the desensitising properties of the EAA receptor types and their uneven distribution in the cortex may reflect the functional pre-requisites of the receptors. These differences may also underlie the tendency to observe desensitisation to EAAs more readily when they are applied to the superficial cortical layers (either topically or iontophoretically)than when applied to the deep layers by iontophoresis (Curtis et al., 1960; Krnjević and Phillis, 1963; Addae and Stone, 1986).

Demonstration of desensitisation to EAAs suggests that it could be possible to protect a neurone from excessive intracortical glu without markedly disturbing its reactivity to synaptic transmission e.g. without disturbing the single cell firing rate or the cortical evoked potentials(Addae and Stone, 1986). Conceivably EAA (particularly one acting at the quisqualate receptor site) could be used to enhance desensitisation of the neurone to endogenous EAAs and thereby contribute to the prevention and cure of some of the EAA-induced neurological disorders.

REFERENCES

ABDUL-GHANI, A.S., BRADFORD, H.F., COX, D.W.G. & DODD, P.R. (1979) Peripheral sensory stimulation and the release of transmitter amino acids in vivo from specific regions of cerebral cortex. Brain Res. 171: 55-56.

ADDAE, J.I. & STONE, T.W. (1986) Effects of topically applied excitatory amino acids on evoked potential and single cell activity in rat cerebral cortex. Eur. J. Pharmacol. 121:337-343.

ADDAE, J.I. & STONE, T.W. (1987) Interactions between topically applied excitatory amino acids on rat cerebral cortex: discrimination by pentobarbitone. Exp. Brain Res. 68: 613-618.

ADDAE, J.I. & STONE, T.W. (1987) Involvement of N-methyl-D-aspartate receptors in the augmenting response in rat neocortex. Neurosci Lett. 78:323-327.

ADDAE, J.I. & STONE, T.W. (In Press) Effects of anticonvulsants on topically applied excitatory amino acids in the rat cerebral cortex. Gen. Pharmacol.

ARTOLA, A. & SINGER, W. (1987) Long term potentiation and NMDA receptors in rat visual cortex. Nature 330:649-652.

ASSUMPÇÃO, J.A., BERNARDI, N., BROWN, J. & STONE, T.W. (1979) Selective antagonism by benzodiazepines of neuronal responses to excitatory amino acids in the cerebral cortex. Br. J. Pharmac. 67: 563-568.

BAUDRY, M., EVANS, J. & LYNCH, G. (1986) Excitatory amino acids inhibit stimulation of phosphatidylinositol metabolism by aminergic agonists in hippocampus. Nature, 319: 329-331.

BAUGHMAN, R.W. & GILBERT, C.D. (1981) Aspartate and glutamate as possible neurotransmitters in the visual cortex. J. Neurosci. 1: 427-439.

BEAL, M.F., KOWALL, N.W., ELLISON, D.W., MAZUREK, M.F., SWARTZ, K.J. & MARTIN, J.B. (1986) Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. Nature, 321: 168-171.

BENJAMIN, A.M. & QUASTEL, J. (1976) Cerebral uptakes and exchange diffusion in vitro of L- and D- glutamates. J. Neurochem. 26: 431-441.

BENNETT, D.A., BERNARD, P.S., AMRICK, C.K. (1988) A

comparison of PCP-like compounds for NMDA antagonism in two In Vivo models. Life Sci. 42: 447-454.

BENVENISTE, A., DREJER, J., SCHOUSBOE, A. & DIEMER, N.H. (1984) Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischaemia monitored by intracerebral microdialysis. J. Neurochem. 43: 1369-1374.

BERDICHEVSKY, E., RIVEROS, N., SANCHEZ-ARMASS, S. & ORREGO, F. (1983) Kainate, N-methylaspartate and other excitatory amino acids increase calcium influx into rat brain cortex cells in vitro. Neurosci. Lett. 36: 75-80.

BERL, S., LAJTHA, T. & WAELSCH, H. (1961) Amino acid and protein metabolism - VI. Cerebral compartments of glutamic acid metabolism. J. Neurochem. 7: 186-197.

BERNSTEIN, J. & FISHER, R.S. (1985) Excessive glutamate as an inhibitor of excitatory transmission in rat hippocampal slices. Neurosci. Lett. 61: 19-24.

BISCOE, T.J., EVANS, R.H., FRANCIS, A.A., MARTIN, M.R., WATKINS, J.C., DAVIES, J. & DRAY, A. (1977) D-α-aminoadipate as a selective antagonist of amino acid-induced and synaptic excitation of mammalian spinal neurones. Nature, 270: 743-745.

BLOOMFIELD, S.A. & DOWLING, J.E. (1985) Roles of aspartate and glutamate in synaptic transmission in rabbit retina. I. outer plexiform layer. J. Neurophysiol. 53: 699-713.

BONHAUS, D.W., BURGE, B.C., McNAMARA J.O. (1987) Biochemical evidence that glycine allosterically regulates an NMDA receptor-coupled ion channel. Eur. J. Pharmacol. 14: 489-490.

BOWEN, D.M., SMITH, C.C.T. & DAVISON, A.N. (1983) Excitotoxicity in ageing and dementia. In: Excitotoxins, exd. Fluxe, K., Roberts, P. & Schwarcz, R., pp.354-362, Wenner-Gren International Symposium Series, vol.39.

BRADFORD, H.F., BENNETT, G.W. & THOMAS, A.J. (1973) Depolarizing stimuli and the release of physiologically active amino acids from suspension of mammalian synaptosomes. J. Neurochem. 21: 495-505.

BRADFORD, H.F., CROWDER, J.M. & WHITE, E.J. (1986) Inhibitory actions of opiod compounds on calcium fluxes and neurotransmitter release from mammalian cerebral cortex slices. Br. J. Pharmac. 88: 87-93.

BRADFORD, H.F. & McILWAIN, H. (1966) Ionic basis for the depolarization of cerebral tissues by excitatory acidic amino acids. J. Neurochem. 13: 1163-1177.

BRADFORD, H.F. & WARD, H.K. (1976) On glutaminase activity in

mammalian synaptosomes. Brain Res. 110: 115-125.

BRADFORD, H.F., WARD, H.K. & THOMAS, A.J. (1978) Glutamine - a major substrate for nerve endings. J. Neurochem. 30: 1453-1459.

BRAITMAN, D.J. (1986) Desensitization to glutamate and aspartate in rat olfactory (prepyriform) cortex slice. Brain Res. 364: 199-203.

CHAPMAN, A.G., ENGELSEN B., MELDRUM, B.S. (1987) 2-Amino-7-phosphonoheptanoic acid inhibits insulin-induced convulsions and striatal aspartate accumulation in rats with frontal cortical ablation.

CHOI, D.W. (1985) Two mechanisms underlying glutamate neurotoxicity in cortical cell culture. Soc. Neurosci. Abstr. 11: 153.

CHOI, D.W., PETERS, S., VISESKUL, V. (1987) Dextrorphan and Levorphanol selectively block N-methyl-D-aspartate receptor-mecdiated neurotoxicity on cortical neurons. J. Pharmacol. Exp. Ther. 242: 713-720.

CLARK, R.M. & COLLINS, G.G.S. (1976) The release of endogenous amino acids from the rat visual cortex. J. Physiol. 262: 383-400.

COAN, E.J. & COLLINGRIDGE, G.L. (1985) Magnesium ions block an N-methyl-D-aspartate receptor mediated component of synaptic tranmsission in rat hippocampus. Neurosci. Lett. 53: 21-26.

COLLINS, G.G.S. (1980) Release of endogenous amino acid neurotransmitter candidates from rat olfactory cortex slices: possible regulatory mechanisms and the effects of pentobarbitone. Brain Res. 190: 517-528.

COLLINS, G.G.S. & SURTEES, L. (1986) "Desensitization" of excitatory amino acid responses in the rat olfactory cortex. Neuropharmacology 25: 231-240.

COMPTON, R.P., CONTERAS, P.C., O'DONOHUE., T.L., MONAHAN, J.B. (1987) The N-methyl-D-aspartate antagonist, 2-amino-7-phosphonoheptanoate, produces phencyclidine-like behavioral effects in rats. Eur. J. Pharmacol. 136: 133-134.

CONTI, F., RUSTIONI, A., PETRUSZ, P., TOWLE, A.C. (1987) Glutamate-positive neurons in the somatic sensory cortex of rats and monkeys. J. Neurosci 7: 1887-1901.

COYLE, J.T., BIRD, S.J., EVANS, R.H., GULLEY, R.L., NADLER, J.V., NICKLAS, W.J., OLNEY, J.W., SCHMITT, F.O. & WORDEN, F.G. (1981) Excitatory amino acid neurotoxins. neurosci. Res. Prog. Bull. 19: 331-429.

COYLE, J.T., & SCHWARZ, R. (1976) Lesion of striatal neurones with kainic acid provides a model for Huntington's chorea. Nature 263: 244-246.

CROSS, A.J., SLATER, P., SIMPSON, M., ROYSTON, C., DEAKIN, J.F.W., PERRY, R.H. & PERRY, E.R. (1987) Sodium dependent D-[3H]aspartate binding in cerebral cortex in patients with Alzheimer's and Parkinson's disease. Neurosci Lett. 79: 213-217.

CROUCHER, M.J., COLLINS, J.F. & MELDRUM, B.S. (1982) Anticonvulsant action of excitatory amino acid antagonists. Science 216: 899-901.

CROWDER, J.M. & BRADFORD, H.F. (1987) Common anticonvulsants inhibit Ca++ uptake and amino acid neurotransmitter release in vitro. Epilepsia 28: 378-382.

CULL-CANDY, S.G. & OGDEN, S.C. (1985) Ion channels activated by L-glutamate and GABA in cultured cerebellar neurones of the rat. Proc. Roy. Soc. Lond. B224: 367-373.

CULL-CANDY S.G., & USOWICZ, M.M. (1987) Multuple-conductance channels activated by excitatory amino acids in cerebellar neurons. Nature, 325: 525-528.

CUNNINGHAM, J.R. & NEAL, M.J. (1985) Effect of excitatory amino acids on γ-aminobutyric acid release from frog horizontal cells. J. Physiol. 362: 51-67.

CURTIS, D.R., PHILLIS, J.W. & WATKINS, J.C. (1959) Chemical excitation of spinal neurones. Nature, 183: 611-612.

CURTINS, D.R., PHILLIS, J.W. & WATKINS, J.C. (1960) The chemical excitation of spinal neurones by certain acidic amino acids. J. Physiol. 150: 656-682.

CZUCWAR, S.J. & MELDRUM, B. (1982) Protection against chemically-induced seizures by 2-amino-7-phosphonoheptanoic acid. Eur. J. Pharmac. 83: 335-338.

DAGANI, F. & ESECINSKA, M. (1987) Relationship among ATP synthesis, K+ gradients, and neurotransmitter amino acid levels in isolated rat brain synaptosomes.

DAVIES, J., EVANS, R.H., FRANCIS, A.A., JONES, A.W. & WATKINS, J.C. (1981a) Antagonism of excitatory amino acid-induced and synaptic excitation of spinal neurones by cis-2,3,-piperidine dicarboxylate. J. Neurochem. 36: 1305-1307.

DAVIES, J., EVANS, R.H., JONES, A.W., MEWETT, K.N., SMITH, D.A.S. & WATKINS, J.C. (1983) Recent advances in the pharmacology of excitatory amino acids in the mammalian central nervous system. In: Exctiotoxins, ed. Fuxe, K., Roberts, P. & Schwarcz, R., pp.43-54. Wenner-Gren International Symposium

Series, vol. 39, London: Macmillan.

DAVIES, J., EVANS, R.H., HERLING, P.L., JONES, A.W., OLVERMAN, H.J., POOK, P., WATKINS, J.C. (1986) CPP, a new potent and selective NMDA antagonist-depression of central neuron responses, affinity for [^{3}H]D-AP5 binding-sites on brain membranes and anticonvulsant activity. Brain Res. 382: 169-173.

DAVIES, J., FRANCIS, A.A., JONES, A.W. & WATKINS, J.C. (1981) 2-amino-5-phosphonovalerate (APV), a potent and selective antagonist of amino acid-induced and synaptic excitation. Neurosci. Lett. 21: 77-81.

DAVIES, J. & WATKINS, J.C. (1977) Effect of magnesium ions on the response of spinal neurones to excitatory amino acids and acetylcholine. Brain Res. 130: 364-368.

DAVIES, J. & WATKINS, J.C. (1979) Selective antagonism of amino acid-induced and synaptic excitation in the cat spinal cord. J. Physiol. 297: 621-635.

DAVIES, J. & WATKINS, J.C. (1985) Depressant actions of -D-glutamylaminomethyl sulfonate (GAMS) on amino acid-induced and synaptic excitation in the cat spinal cord. Brain Res. 327: 113-120.

DAVIES, L.P. & JOHNSTON, G.A.R. (1976) Uptake and release of D- and L-aspartate by rat brain slices. J. Neurochem. 26: 1007-1014.

DE ROBERTIS, E. & DE PLAZAS, F.S. (1976) Isolation of hydrophobic proteins binding amino acids. Stereoselectivity of the binding of L-[^{14}C] glutamic acid in cerebral cortex. J. Neurochem. 26: 1237-1243.

DINGLEDINE, R. (1983) N-methyl aspartate activates voltage-dependent calcium conductance in rat hippocampal pyramidal cells. J. Physiol. 343: 385-405.

DREJER, J., BENVENISTE, H., DIEMER, N.H. & SCHOUSBOE, A. (1985) Cellular origin of ischeamia-induced glutamate release from brain tissue in-vivo and in-vitro. J. Neurochem. 45: 145-151.

DREJER, J. & HONORE, T. (1987) Phencyclidine analogues inhibit NMDA-stimulated [^{3}H] GABA release from cultured cortex neurones. Eur. J. Pharmacol. 143: 287-290.

DOWNING, J.E.G. & ROLE, L.W. (1987) Activators of protein kinase C enhance acetylchloline receptor desensitization in sympathetic ganglion neurones. Proc. Natl. Acad. Sci. USA 84: 7739-7743.

DYKENS, J.A., STERN, A. & TRENKNER, E. (1987). Mechanism of kainate toxicity to cerebellar neurons in vitro is analogous to reperfusion tissue injury. J. Neurochem. 49(4): 1222-1228.

DUX, E., MIES, G., HASSMANN, K.A. & SIKLOS, L. (1987) Calcium in the mitochondria following brief ischemia of gerbil brain. Neurosci. Lett. 78: 295-300.

ENGBERG, I., FLATMAN, J.A. & LAMBERT, J.D.C. (1978) The action of N-methyl-D-aspartic and kainic acids on mononeurones with emphasis on conductance changes. Br. J. Pharmac. 64: 384-385p.

ENGBERG, I., FLATMAN, J.A. & LAMBERT, J.D.C. (1979) The actions of excitatory amino acids on motoneurones in the feline spinal cord. J. Physiol. 288: 227-261.

ERECIŃSKA, M. (1987) The neurotransmitter amino acid transport systems. A fresh outlook on an old problem. Biochem. Pharmacol. 36: 3547-3555

ERECIŃSKA, M., NELSON, D., WILSON, D.F. & SILVER, I.A. (1984) Neurotransmitter amino acids in the CNS.I. Regional changes in amino acid levels in rat brain during ischaemia and reperfusion. Brain Res. 304: 9-22.

ERECIŃSKA, M., TROEGER, M.B., WILSON, D.F. & SILVER, I.A. (1986) The role of glial cells in regulation of neurotransmitter amino acids in the external environment. II. Mechanism of aspartate transport. Brain Res. 369: 203-214.

EUSEBI, F., MOLINARO, M. & ZANI, B.M. (1985) Agents that activate protein kinase C reduce acetylcholine sensitivity in cultured myotubes. J. Cell Biol. 100: 1339-1342.

EVANS, R.H., FRANCIS, A.A., HUNT, K., OAKES, D.J. & WATKINS, J.C. (1979) Antagonism of excitatory amino acid-induced responses and of synaptic excitation in the isolated spinal cord of the frog. Br. J. Pharmac. 67: 591-603.

EVANS, R.H., FRANCIS, A.A. & WATKINS, J.C. (1977) Selective antagonism by Mg^{++} of amino acid-induced depolarization of spinal neurones. Experientia 33: 489-491.

FAGG, G.E. (1987) Phencyclidine and related drugs bind to the activated N-methyl-D aspartate receptor-channel complex in rat brain membranes. Neurosci. Lett. 76: 221-227.

FAGG, G.E. & MATUS, A. (1984) Selective association of N-methyl aspartate and quisqualate types of L-glutamate receptor with brain postsynaptic densities. Proc. Natl. Acad. Sci. USA 81: 6876-6880.

FAGNI, L., BAUDRY, M. & LYNCH, G. (1983a) Desensitization to glutamate does not affect synaptic transmission in rat hippocampal slices. Brain Res. 261: 167-171.

FAGNI, L., BAUDRY, M. & LYNCH, G. (1983b) Classification and properties of acidic amino acid receptors in hippocampus. I.

Electrophysiological studies of an apparent desensitization and interactions with drugs which block transmission. J. Neurosci. 3: 1538-1546.

FAGNI, L., BAUDRY, M. & LYNCH, G. (1984) Intracellular studies of an apparent desensitization of excitatory amino acid receptors in hippocampal slices. Soc. Neurosci. Abstr. 10: 229.

FONNUM, F. (1984) Glutamate: a neurotransmitter in mammalian brain. J. Neurochem. 42: 1-11.

FOSTER, A.C., & FAGG, G.E. (1984) Acidic Amino acid binding sites in mammalian neuronal membranes: their characteristics and relationship to synaptic receptors. Brain Res. Reviews 7:103-164.

FOSTER, A.C., COLLINS, J.F. & SCHWARCZ, R. (1983) On the excitotoxic properties of quinolinic acid, 2,3-piperidine dicarboxylic acid and structurally related compounds. Neuropharmacology 22: 1331-1342.

FRANCIS, A.A., JONES, A.W. & WATKINS, J.C. (1980) Di-peptide antagonists of amino acid-induced and synaptic excitation in the frog spnal cord. J. Neurochem. 35: 1458-1460.

FUKUDA, H., TANAKA, T., KAIJIMA, M., NAKAI, H. & YONEMASU, Y. (1985) Quisqualic acid-induced hippocampal seizures in unanaesthetized cats. Neurosci. Lett. 59: 53-59.

GANONG, A.H., LANTHORN, T.H. & COTMAN, C.W. (1983) Kynurenic acid inhibits synaptic and acidic amino acid-induced responses in the rat hippocampus and spinal cord. Brain Res. 273: 170-174.

GENT, J.P. & WACEY, T.A. (1983) The effects of chlormethiazole on single unit activity in rat brain: interactions with inhibitory and excitatory neurotransmitters. Br. J. Pharmac. 80: 439-444.

GREENAMYRE, J.T., OLSON, J.M.M., PENNEY, J.B. & YOUNG, A.B. (1985a) Autoradiographic characterisation of N-methyl-D-aspartate-, quisqualate-, and kainate-sensitive glutamate binding sites. J. Pharmac. Exper. Ther. 233: 254-263.

GREENAMYRE, J.T., PENNEY, J.B., YOUNG, A.B., D'AMATO, C.J., HICKS, S.P. & SHOULSON, I. (1985b) Alterations in L-glutamate binding in Alzheimer's and Huntington's diseases. Science, 227: 1496-1499.

GRIFFITHS, T., EVANS, M.C. & MELDRUM, B.S. (1983) Temporal lobe epilepsy, excitotoxins and the mechanism of selective neuronal loss. In: Excitotoxins, ed. Fuxe, K., Roberts, P. & Schwarcz, R., pp.331-342. Wenner-Gren International Symposium Series, vol. 39. London: Macmillian.

HABLITZ, J.J. & LANGMOEN, I.A. (1982) Excitation of

hippocampal pyramidal cells by glutamate in the guinea-pig and rat. J. Physiol. 325: 317-331.

HAGBERG, H., ANDERSON, P., KJELLMER, I., THRINGER, K. & THORDSTEIN, M. (1987) Extracellular overflow of glutamate, aspartate, GABA and taurine in the cortex and basal ganglia of fetal lambs during hypoxia-ischemia. Neurosci. Lett. 78: 311-317.

HALL, J.G., HICKS, T.P., McLENNAN, H., RICHARDSON, T.L. & WHEAL, H.V. (1979) The excitation of mammalian central neurones by amino acids. J. Physiol. 286: 29-39.

HAMBERGER, A.C., HAN CHIANG, G., NYLEN, E.S., SCHEFF, S.W. & COTMAN, C.W. (1979) Glutamate as a CNS transmitter. I. Evaluation of glucose glutamine as precursors for the synthesis of preferentially released glutamate. Brain Res. 168: 513-530.

HARRISON, N.L. (1985) Pentobarbitone as an excitatory amino acid antagonist in slices of rat cerebral cortex. J. Physiol. 360: 38p.

HARRISON, N.L. & SIMMONDS, M.A. (1985) Quantative studies of some antagonists of N-methyl-D-aspartate in slices of rat cerebral cortex. Br. J. Pharmac. 84: 381-391.

HAUPTMAN, M., NELSON, D., WILSON, D.F. & ERECIŃSKA, M. (1984) Neurotransmitter amino acid levels in rat brain synaptosomes during and after in vitro anoxia and simulated ischaemia. Brain Res. 304: 23-25.

HERRLING, P.L. (1985) Pharmacology of the corticocaudate excitatory postsynaptic potential in the cat: evidence for its mediation by quisqualate- or kainate-receptors. Neuroscience, 14: 417-426.

HERTEL, C. & PERKINS, J.P. (1984) Receptor-specific mechanisms of desensitization of β-adrenergic receptor function. Molec. Cell Endocrinol. 37: 245-256.

HICKS, T.P. & GUEDES, R.C.A. (1983) Neuropharmacological properties of electrophysiologically identified visually responsive neurones of the posterior lateral suprasylvian area. Exper. Brain Res. 49: 157-173.

HICKS, T.; GUEDES, R.C.A.; CREUTZFELT, O.D. (1981) Selective synaptic antagonism by atropine and α-aminoadipate of pulvinar and cortical afferents to the suprasylvian visual area (Clare-Bishop area) Brain Res. 208: 456-462.

HONEY, C.R., MILJKOVIC, Z., MACDONALD, J.F. (1985) Ketamine and phencyclidine cause a voltage-dependent block of responses to L-aspartic acid. Neurosci. Lett. 61: 135-139.

HUETTNER, E. & BAUGHMAN, R.W. (1985) Response properties of

identified cortical neurons in tissue culture to excitatory amino acid agonists and antagonists. Soc. Neurosci. Abstr. 11: 823.

HU G.Y., HVALBY, Q, WALAAS, S.L., ALBERT, K.A., SKJEFLO, P., ANDERSEN, P., GREENGARD, P. (1987) Protein kinase C injection into hippocampal pyramidal cells elicits features of long term potentiation. Nature, 328: 426-429.

ISHIDA, A.T. & NEYTON, J. (1985) Quisqualate and L-glutamate inhibit retinal horizontal-cell response to kainate. Proc. Natl. Acad. Sci. USA 82: 1837-1841.

JAHR, C.E. & STEVENS, C.F. (1987) Glutamate activates multiple single channel conductances in hippocampal neurons. Nature, 325: 522-525.

JANSCO, G., KARCSU, S., KIRALY, E., SZEBENI, L., TOTH, E., BACRY, E., JOO, F. & PARDUCZ, A. (1984) Neurotoxin induced cell nerve degeneration: possible involvement of calcium. Brain Res. 295: 211-216.

JASPER, H.H. & KOYAMA, I. (1969) Rate of release of amino acids from the cerebral cortex in the cat is affected by brainstem and thalmic stimulation. Can. J. Physiol. Pharmac. 47: 889-905.

JAVITT, D.C., JOTKOWITZ, A., SIRCAR, R., & ZUKIN, S.R. (1987) Non-competitive regulation of phencyclidine/σ-receptors by the N-methyl-D-aspartate receptor antagonist D-(-)-2-amino-5-phosphonovaleric acid. Neurosci. Lett. 78: 193-198.

JOHNSON, J.W. & ASCHER, P. (1987) Glycine potentiates the NMDA response in cultured mouse brain neurons. Nature, 325: 529-531.

KATZ, B. & THESLEFF, S. (1957) A study of the "desensitization" produced by acetylcholine at the motor end-plate. J. Physiol. 138: 63-80.

KINSCHERF, D.A., CHANG, M.M., RUBIN, E.H., SCHNEIDER, D.R. & FERRENDELLI, J.A. (1976) Comparison of the effects of depolarizing agents and neurotransmitters on regional CNS cyclic GMP levels in various animals. J. Neurochem. 26: 527-530.

KISKIN, N.I., KRISHTAL, A.O. & TSYNDRENKO, A.Y. (1986) Excitatory amino acid receptors in hippocampal neurons: kainate fails to desensitize them. Neurosci. Lett. 63: 225-230.

KLEINSCHMIDT, A., BEAR, M.F., SINGER, W. (1987) Blockade of "NMDA" receptors disrupts experience-dependent plasticity of kitten striate cortex. Science, 238: 355-358.

KNOPFEL, T., ZEISE, M.L., CUÉNOD, M., ZIEGLGÄNSBERGER (1987) L-homocysteic acid but not L-glutamate is an endogenous N-methyl-d-aspartic acid receptor preferring agonist in rat

neocortical neurons in vitro. Neurosci. Lett. 81: 188-192.

KOEK, W., WOODS, J.H., MATTSON, M.V., JACOBSON, A.E. & MUDAR, P.J. (1987) Excitatory amino acid antagonists induce a phencyclidine-like catalepsy in pigeons: structure-activity studies. Neuropharm. 26: 1261-1266.

KRNJEVIĆ, K. & PHILLIS, J.W. (1963) Iontophoretic studies of neurones in the mammalian cerebral cortex. J. Physiol. 165: 274-304.

LAPIN, I.P. (1981) Kynurenines and seizures. Epilepsia 22: 257-265.

LEACH, M.J., MARDEN, C.M. & CANNING, H.M. (1986) (+)-cis-2,3-piperidine dicarboxylic acid is a partial N-methyl-D-aspartate agonist in the in vitro rat cerebellar cGMP model. Eur. J. Pharmac. 121: 173-179.

LEHMANN, J., FERKANY, J.W., SCHAEFFER, P. & COYLE, J.T. (1985) Dissociation between the excitatory and "excitotoxic" effects of quinolinic acid analogs on striatal cholinergic interneuron. J. Pharmac. Exper. Ther. 232: 873-882.

LEWIS, M.R., GALLAGHERM, J.P. & SHINNICK-GALLAGHER, J. (1985) a putative Gl excitatory amino acid receptor mediates vestibular afferent transmission in rats. Soc. Neurosci. Abstr. 11: 104.

LODGE, G. & ANIS, N.A. (1982) Effects of phencyclidine on excitatory amino acid activation of spinal interneurones in the cat. Eur. J. Pharmac. 77: 203-204.

LODGE, D., CURTIS, D.R., JOHNSTON, G.A.R. & BORNSTEIN, J.C. (1980) In vivo inactivation of quisqualate: studies in cat spinal cord. Brain Res. 182: 491-495.

LODGE, D. & JOHNSTON, G.A.R. (1985) Effect of ketamine on amino acid-evoked release of acetylcholine from rat cerebral cortex in vitro. Neurosci. Lett. 56: 371-375.

LOO, P., BRAUNWALDER, A., LEHMANN, J., WILLIAMS, M. (1986) Radioligand binding to central phecyclidine recognition sites is dependent on excitatory amino acid receptor agonists. Eur. J. Pharmac. 123: 467-468.

LUINI, A., GOLDBERG, O. & TEICHBERG, V.I. (1981) Distinct pharmacological properties of excitatory amino acid receptors in the rat striatum: study by Na^+ efflux assay. Proc. Natl. Acad. Sci. USA 78: 3250-3254.

MacDONALD, J.F., MILJKOVIC, Z. & PENNEFATHER, P. (1987) Use-dependent block of excitatory amino acid currents in cultured neurons by ketamine. J. Neurophysiol. 58: 251-261

MacDONALD, J.F. & PORIETIS, A.V. (1982) DL-quisqualic and L-

aspartic acids activates spearate excitatory conductances in cultured spinal cord neurons. Brain Res. 245: 175-178.

MacDONALD, J.F. & WOJTOWICZ, J.M. (1982) The effects of L-glutamate and its analogues upon the membrane conductance of central murine neurones in culture. Can. J. Physiol. Pharmac. 60: 282-296.

MANTHEY, A.A. (1966) The effect of calcium on the desensitisation of membrane receptors at the neuro-muscular junction. J. Gen. Physiol. 49: 963-976.

MARAGOS, W.F., CHU, D.C.M., GREENAMYRE, J.T., PENNY, J.B. & YOUNG, A.B. (1986) High correlation between the localisation of [^{3}H] TCP binding and NMDA receptors. Eur. J. Pharmac. 123: 173-174.

MARTIN, D. & LODGE, D. (1985) Ketamine acts as a non-competitive N-methyl-D-aspartate antagonist on frog spinal cord in vitro. Neuropharmacology, 24: 999-1003.

MAYER, M.L., MacDERMOTT, G.L., SMITH, S.J., BARKER, J.L. (1987) Agonist and voltage-gated calcium entry in cultured mouse spinal cord neurons under voltage clamp measured using arsenazo III. J. Neurosci. 7: 3230-3244.

MAYER, M.L. & WESTBROOK, G.L. (1984) Mixed-agonist action of excitatory amino acids on mouse spinal cord neurones under voltage clamp. J. Physiol. 354: 29-53.

MAYER, M.L. & WESTBROOK, G.L. (1985) The action of N-methyl-D-aspartic acid on mouse spinal neurones in culture. J. Physiol. 361: 65-90.

McLENNAN, H. (1983) Receptors for the excitatory amino acids in the mammalian central nervous system. Prog. Neurobiol. 20: 251-271.

McLENNAN, H. & LODGE, D. (1979) The action of D- -amino-adipate on excitatory amino acid receptors of rat thalmic neurones. Brain Res. 169: 83-90.

MELDRUM, B.S., CROUCHER, M.J., BADMAN, G. & COLLINS, J.F. (1983a) Antiepileptic action of excitatory amino acid antagonists in the photosensitive baboon, Papio papio. Neurosci. lett. 39: 101-104.

MINCHIN, M.C.W. & FONNUM, F. (1979) The metabolism of GABA and other amino acids in rat substantia nigra slices following lesions of the striato-nigral pathway. J. Neurochem. 32: 203-210.

MITCHELL, J.F. (1975) Collection techniques. In: Methods in Brain Research, ed. Bradley, P.B., pp. 295-332. Chichester: John Wiley & Sons.

MONAGHAN, D.T. & COTMAN, C.W. (1982) The distribution of 3H kainic acid binding sites in rats CNS as determined by autoradiography. Brain Res. 252: 91-100.

MONAGHAN, D.T., YAO, D. & COTMAN, C.W. (1984a) Distribution of [3H] AMPA binding sites in rat brain as determined by quantitative autoradiography. Brain Res. 324: 160-164.

MONAGHAN, D.T., YAO, D. & COTMAN, C.W. (1985) L-[^{3}H] glutamate binds to kainate-, NMDA-sensitive binding sites: an autoradiographic analysis. Brain Res. 340: 378-383.

MONAHGHAN, D.T., YAO, D., OLVERMAN, H.J., WATKINS, J.C. & COTMAN, C.W. (1984b) Autoradiography of -D-2-[3H] amino-5-phosphonopentoate binding sites in rat brain. Neurosci. Lett. 52: 253-258.

MORONI, F., LOMBARDI, G., MONETI, G. & ALDINIO, C. (1984) The excitotoxin quinolinic acid is present in the brain of several mammals and its cortical content increases during the aging process. Neurosci. Lett. 47: 51-55.

MURALI MOHAN, P., & SASTRY, B.R. (1985) Calcium and unit response decrement to locally applied glutamate on rat hippocampal CA1 neurons. Eur. J. Pharmac. 114: 335-341.

MURPHY, S.N., THAYER, S.A., MILLER, R.J. (1987) The effects of excitatory amino acids on intracellular calcium in single mouse striatal neurons in vitro. J. Neurosci 7: 4145-4158.

NAITO, S. & UEDA, T. (1983) Adenosine triphosphate-dependent uptake of glutamate into protein I-associated synaptic vesicles. J. Biol. Chem. 258: 696-699.

NAITO, S. & UEDA, T. (1985) Characterization of glutamate uptake into synaptic vesicles. J. Neurochem. 44: 99-109.

NASTUK, W.L. & PARSONS, R.L. (1970) Factors in the inactivation of postjunctional membrane receptors of frog skeletal muscle. J. Gen. Physiol. 56: 218-249.

NICHOLLS, D.G. & SIHRA, T.S. (1986) Synaptosomes possess an exocytotoic pool of glutamate. Nature, 321: 772-773.

NICOLETTI, F., IADOROLA, M.J., WROBLEWSKI, J.T. & COSTA, E. (1986a) Excitatory amino acid recognition sites coupled with inositol phospholipid metabolism: developmental changes and interaction with 1-adrenoceptors. Proc. Natl. Acad. Sci. USA 83: 1931-1935.

NICOLETTI, F., MEEK, J.L., IADAROLA, M.J., CHUANG, D.M., ROTH, B.L. & COSTA, E. 1986b) coupling of inositol phospholipid metabolism with excitatory amino acid recognition sites in rat hippocampus. J. Neurochem. 46: 40-46.

NOVELLI, A. & HENNEBERRY, R.C. 91985) Veratrine- and glutamate-stimulated cGMP production in cultured rat neurons is differentially inhibited by imipramine. Eur. J. Pharmac.118: 189-190.

NOWAK, L.M. & ASCHER, P. (1984) N-methyl-D-aspartic, kainic and quisqualic acids evoked currents in mammalian central neurones. Soc. Neurosci. Abstr. 10: 23.

NOWAK, L.M., BREGESTOWSKI, P., ASCHER, P., HERBERT, A. & PROCHIANTZ, A. (1984) Magnesium gates glutamate-activated channels in mouse central neurones. Nature, 307: 462-463.

OLDENDORF, W.H. (1971) Brain uptake of radiolabelled amino acids, amines and hexoses after arterial injection. Am. J. Physiol. 221: 1629-1639.

OLDENDORF, W.H. & SZABO, J. (1976) Amino acid assignment to one of three blood-brain barrier amino acid carriers. Am. J. Physiol. 230: 94-98.

OLNEY, J.W. (1971) glutamate-induced neuronal necrosis in the infant mouse hypothamamus. J. Neuropath. Exper. Neurol. 30: 75-90.

OLNEY, J.W. & DE GUBAREFF, T. (1978) Glutamate neurotoxicity and Huntington's chorea. Nature, 271: 557-559.

OLNEY, J.W., PRICE, M.T., SAMSON, L. & LABRUYERE, J. (1986) The role of specific ions in glutamate neurotoxicity. Neurosci. Lett. 65: 65-71.

OLVERMAN, H.J., JONES, A.W. & WATKINS, J.C. (1984) L-glutamate has higher affinity than other amino acids for [3H]-D-AP5 binding sites in rat brain membranes. Nature, 307: 460-462.

O'NEILL, K.A., LIEBMAN, J.M. (1987) Unique behavioral effects of the NMDA antagonist, CPP, upon injection into the medial pre-frontal cortex of rats. Brain Res. 435: 371-376.

ORREGO, F. (1979) Criteria for identification of central neurotransmitters, and their application to studies with some nerve preparations in vitro. Neuroscience 4: 1037-1057.

OTTERSEN, O.P., FISCHER, B.O. & STORM-MATHISEN, J. (1983) Retrograde transport of D-[3H] aspartate in thalamocortical neurones. Neurosci. Lett. 42: 19-24.

PASTUSZKO, A., WILSON, D.F. & ERECIŃSKA, M. (1984) Effects of kainic acid in rat brain synaptosomes: the involvement of calcium. J. Neurochem. 43: 747-754.

PEINADO, J.M., IRIBAR, M.C., MYERS, R.D. (1987) Hemidecortication selectively alters release of glutamate in perfusates collected from cerebral cortex of unrestrained rats.

Neurochem. Res. 12: 629-634.

PERKINS, M.N. & STONE, T.W. (1982) An iontophoretic investigation of convulsant kynureines and their interaction with the endogenous excitant quinolinic acid. Brain Res. 247: 184-187.

PERKINS, M.N., STONE, T.W., COLLINS, J.F. & CURRY, K. (1981) Phosphonate analogues of carboxylic acids as amino acid antagonists on rat cortical neurones. Neurosci. Lett. 23: 333-336.

PETERS, S., KOH, J., & CHOI, D.W. (1987) Zinc selectively blocks the action of N-methyl-D-aspartate on cortical neurones. Science, 236: 589-592.

POTASHNER, S.J. (1978) The spontaneous and electrically-evoked release from slices of guinea-pig cerebral cortex of endogenous amino acids labelled via metabolism of D-[U-14] glucose. J. Neurochem. 31: 177-186.

RĒCASENS, M., SASSETTI, I., NOURIGAT, A., SLADECZEK, F., BOCKAERT, J. (1987) Characterization of subtypes of excitatory amino acid receptors involved in the stimulation of inositol phosphate synthesis in rat brain synaptoneurosomes. Eur. J. Pharmacol. 141: 87-94.

REYNOLDS, I.J., MURPHY, S.N., MILLER, R.J. (1987) 3H-labelled MK-801 binding to the excitatory amino acid receptor complex from rat brain is enhanced by glycine. Proc. Nat l. Acad. Sci., USA, 84: 7744-7748.

RICHARDS, C.D. (1972) On mechanism of barbiturate anaesthesia. J. Physiol. 227: 749-767.

ROBERTS, P.J. (1974a) Glutamate receptors in the rat central nervous system. Nature, 252: 399-401.

ROBERTS, P.J. (1974b) Amino acid release from isolated rat dorsal root ganglia. Brain Res. 74: 327-332.

ROSS, S.M., SEELIG, M., & SPENCER, P.S. (1987) Specific antagonism of excitotoxic action of "uncommon" amino acids assayed in organotypic mouse cortical cultures. Brain Res. 425: 120-127.

ROSS, S.M. & SPENCER, P.S. (1987) Specific antagonism of behavioral action of "uncommon" amino acids linked to motor-system diseases. Synapse, 1: 248-253.

ROTHMAN, S. (1984) Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. J. Neurosci. 4: 1884-1891.

ROTHMAN, S.M. & OLNEY, J.W. (1986) Glutamate and the

pathophysiology of hypoxic-ischemic brain damage. Ann. Neurol. 19: 105-111.

ROTHMAN, S. M., THURSTON, J.H & HAUHART, R.E.(1987) Delayed neurotoxicity of excitatory amino acids in vitro. Neurosci. 22: 471-480.

ROTHMAN, S. M., THURSTON. J. H., HAUHART, R. E., CLARK, G. D., SOLOMON, J.S., (1987), Ketamine protects hippocampal neurons from anoxia in vitro. Neuroscience 21: 673-678.

SANCHEZ-PRIETO, J., SHIRA, T.S., NICHOLLS, D. G. (1987), Characterization of the exocyctotic release of glutamate from guinea pig cerebral cortical synaptosomes. J. Neurochem. 49: 58-64

SANDERSON, C., & MURPHY, S. (1982), Glutamate binding in the rat cerebral cortex during ontogeny. Dev. Brain Res. 2: 329-339.

SARNE, Y. (1976) Desensitization to -aminobutyric acid in crustacean muscle fibres. J. Physiol. 257. 779-790.

SASTRY, B. R. S., & PHILLIPS, J.W. (1976), Antagonism of glutamate and acetylcholine excitation of rat cerebral cortical neurones by diphenylhydantoin. Gen. Pharmac. 7: 411-413.

SAWADA, S. & YAMAMOTO, C., (1985), Blocking action of pentobarbital on receptors for excitatory amino acids in the guinea-pig hippocampus. Exper. Brain Res. 59: 226-231.

SCHMIDT, B., WEISS, S., SEBBEN,M., KEMP, D. E., BOCKAERT, J., SLADECZEK, F., (1987), Dual action of excitatory amino acids on the metabolism of inositol phosphates in striatal neuron. Molecular Pharmacol. 32: 364-368.

SCHOUSBOE, A., SVENNEBY, G. & HERTZ, L. (9177) Uptake and metabolism of glutamate in astrocytes cultured from dissociated mouse brain hemispheres. J. Neurochem. 29: 999-1005.

SCHWARCZ, R., BRUSH, G.S. FOSTER, A.C. & FRENCH, E. D., (1984) Seizure activity and lesions after hippocampal quinolinic acid injection. Exper. Neurol. 84: 1-17.

SCHWARCZ, R.D., SCHOLZ, D. & COYLE, J.T. (1978), Structure activity relations for the neurotoxicity of kainic acid derivatives and glutamate analogues. Neuropharmacology 17: 145-151.

SCHWARCZ, R., WHETSELL, W. O., & MANGANO, R. M., (1983), Quinolinic acid, an endogenous metabolite that produces axon-sparing lesions in rat brain. Science 219: 316-318.

SHANK, R. P., BENNETT, G.S., FREYTAG, S.O. & CAMPBELL, G. L., (1985), Pyruvate carboxylase: an astrocyte-specific enzyme implicated in the replenishment of amino acid neurotransmitter

pools. Brain Res. 329: 364-367.

SHANK, R. P., & CAMPBELL, G. L. (1982), Glutamine and alpha-ketoglutarate uptake and metabolism by nerve terminal enriched material from mouse cerebellum. Neurochem. Res. 7: 601-616.

SILVERSTEIN, F.S., BUCHANAN, K., JOHNSTON, M.V. (1986), Perinatal hyppxia-ischemia disrupts striatal high-affinity [3H] glutamate uptake into synaptosomes. J. Neurochem. 47: 1614-1629.

SHIMIZU, H., ICHISHITA, H., & ODAGIRI, H. (1974), Stimulated formation of C-AMP by aspartate and glutamate in cerebral cortical slices of guinea-pig. J. Biol. Chem. 249: 5955-5962.

SIMON, R. P., SWAN, J. H., GRIFFITHS, T. & MELDRUM, B.S., (1984) Blockade of N-methyl-D-aspartate receptors may protect against ischemic damage in the brain. Science 226: 850-852.

SLADECZEK, F., PIN., J.P., RECASENS, M., BOCKAERT, J. & WEISS, S. (1985) Glutamate stimulates inositol phosphate formation in striatal neurones. Nature 317: 717-7I9

SNODGRASS, S. R. (1983) Receptors for amino acid transmitters. In: Handbook of Psychopharmacology, vol. 17, Biochemical Studies of CNS Receptors. Ed. Iversen, L. L., Iversen, S.D. & Snyder, S.H., pp. 167-240. New York, Plenum Press.

SPENCER, P.S., NUNN, P.B., HUGON, J., LUDOLPH, A.C., ROSS, S.M., ROY, D. N., ROBERTON, R.C. (1987). Guam amyotrophic lateral sclerosis - Parkinsonism - dementia linked to a plant excitant neurotoxin. Science 237: 517-522.

SPENCER, P.S., ROY, D. N. LUNDOLPH, A., HUGON,J., DIVEDI, M.P., SCHAUMBURG, H.H, (1986) Lathyrism, evidence for the role of the neuroexcitatory amino acid, BOAA. Lancet ii: 1066-1067.

STALLCUP, W.B., BULLOCH, K., & BAETGE, E. E. (1979) Coupled transport of glutamate and sodium in a cerebellar nerve cell line. J. Neurochem. 32: 57-65.

STONE, T.W., (1976) Blockade by amino acid antagonists of neuronal excitation mediated by the pyramidal tract. J. Physiol. 257: 187-198.

STONE, T. W., (1979) Amino acids as neurotransmitters of corticofugal neurons in rat: a comparision of glutamate and aspartate. Br. J. Pharmac. 67: 545-551.

STONE. T. W. (1981) Studies with excitatory amino acid antagonists in rat CNS: 2- amino-5-phosphonovaleric acid, phenytoin, and benzodiazepines. In: Amino Acid Neurotransmitters, ed. DeFeudis, F.V & Mandel, P., pp. 223-230. New York, Raven Press.

STONE, T. W., & BURTON, N. R. (1988) NMDA receptors and ligands

in the vertebrate CNS. Progress in Neurobiology 30: 333.

STONE, T.W., PERKINS, M.N., COLLINS., J.F., & CURRY, K. (1981) Activity of the enantiomers of 2-amino-5-phosphonovaleric acid as stererospecific antagonists of excitatory amino acids. Neuroscience 6: 2249-2252.

SURTEES, L. & Collins, G.G.S. (1985) Receptor types mediating the excitatory actions of exogenous L-aspartate and L-glutamate in rat olfactory cortex. Brain Res. 334: 287-295.

TEICHBERG, V. I., TAL, N., GOLDBERG, O. & LUINI, A. (1984) Barbiturates, alcohols and the CNS excitatory neuro-transmittion, specific effects on the kainate and quisqualate receptors. Brain Res. 291: 285-292.

THOMSON, A.M. (1986) A magnesium-sensitive post-synaptic potential in rat cerebral cortex resenbles neuronal responses to N-methylaspartate. J. Physiol. 370: 531-549.

THOMSON, A. M., WEST, D. C. & LODGE, D. (1985), An N-methyl-aspartae receptor-mediated synapse in rat cerebral cortex, a site of action of ketamine? Nature 313: 479-481.

TRIGGLE, D. J. (1981) Desensitization. In: Towards Understanding Receptors, ed. Lamble, J.W., pp 28-33. Amsterdam, Elsevier/North Holland Publishing Co.

TSUMOTO, T., MASUI, H., & SATO, H. (1986) Excitatory amino acid transmitters in neuronal circuits of the cat visual cortex. J. Neurophysiol. 55: 469-483.

UNNERSTALL, J. R. & WAMSLEY, J. K. (1983) Autoradiographic localization of high-affinity [3H] kainic acid binding sites in the rat forebrain. Eur. J. Pharmac. 86: 361-371.

VLACHOVÁ, V., VYKLICKÝ, L., VYKLICKÝ, L., Jr. & VYSKOČIL, F. The action of excitatory amino acids on chick spinal cord neurones in culture. J. Physiol (Lond.) 386: 425-438.

VINCENT, S. R., & McGEER, E. G., (1980) A comparison of sodium dependent glutamate binding with high affinity glutamate uptake in rat striatum. Brain Res. 184: 99-108.

VYKLICKÝ, L.& VYKLICKÝ, L. Jnr. VYSKOČIL, F., VLACHOVÁ, V.,UJEC, E. & MICHL, J. (1986) Evidence that excitatory amino acids not only activate the receptor channel complex but also lead to use-dependent block. Brain Res. 363: 148-151.

WATKINS, J.C. & EVANS, R. H. (1981) Excitatory amino acid tansmitters. Ann. Rev. Pharmac. Toxicol. 21: 165-204.

WATKINS, J.C. (1984) Excitatory amino acids and central synaptic

transmission. Trends in Pharmac. Sci. 5: 373-376.

WEAKLEY, J. N. (1969) Effect of barbiturates on 'quantal' synaptic transmission in spinal motoneurones. J. Physiol. 204: 63-77.

WEILER, C.T., NYSTROM, B. & HAMBERGER, A. (1979) Glutaminase and glutamine synthetase activity in synaptosomes, bulk-isolated glia and neurons. Brain Res. 160: 539-543.

WERMAN, R. (1966) Criteria for identification of a central nervous system transmitter. Comp. Biochem. Physiol. 18: 745-766.

WESTBROOK, G.L, & MAYER, M.L. (1987) Micromolar concentrations of Zn++ antagonize NMDA and GABA responses of hippocampal neurons. Nature, 328: 640-643.

WHEATLEY, P.L. & COLLINS, J.K. (1986) Quantitative studies of N-methyl-D-aspartate, 2-amino-5phosphonovalerate and cis-2,3-piperidine dicarboxylate interaction on the neonatal rat spinal cord in vitro. Eur. J. Pharmacol. 121: 257-263.

WHEELER, D.D. (1987) Are there both low- and high-affinity glutamate transporters in rat cortical synaptosomes? Neurochem. Res., 12: 667-680.

WHEELER, D.D. & HOLLINGSWORTH, R.G. (1978) A model of high affinity glutamic acid transport by cortical synaptosomes from the Long-Evans rat. J. Neurochem. 30: 1311-1319.

WIELOCH, T. (1985) Hypoglycemia-induced neuronal damage prevented by an N-methyl-D-aspartate antagonist. Science, 230: 681-683.

WONG, E.H.F., KEMP, J.A., PRIESTLEY, T., KNIGHT, A.R., WOODRUFF, G.N., IVERSEN, L.L. (1986) The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. Proc. Nat 1. Acad. Sci., USA, 33: 7104-7108.

WOODRUFF, G.N., FOSTER, A.C., GILL, R., KEMP, J.A., WONG, E.H.F. & IVERSEN, L.L. (1987) The interaction between MK-801 and receptors for N-methyl-D-aspartate: functional consequences. Neuropharmacology, 26: 903-910.

WROBLEWSKI, J.T., NICOLETTI, F., FADDA, E., COSTA, E. (1987) Phencyclidine is a negative allosteric modulator of signal transduction at two subclasses of excitatory amino acid receptors. Proc. Nat 1. Acad. Sci., USA, 84: 5068-5072.

WU, K., CARLIN, R. & SIEKEVITZ, P. (1986) Binding of L-[3H] glutamate to fresh or frozen synaptic membrane and postsynaptic density fractions isolated from cerebral cortex and cerebellum of fresh or frozen canine brain. J. Neurochem. 46: 831-841.

ZORUMSKI, C.F. & FISCHBACH, G.D. (1985) Differentiation between glutamate receptors based on desensitisation. Soc. Neurosci. Abstr. 11: 105.

ZUKIN, S.R., ZUKIN, R.S., VALE, W., RIVIER, J., NICHTENHAUSER, R., SNELL, L.D. AND JOHNSON, K.M. (1987) An endogenous ligand of the brain σ/PCP receptor antagonizes NMDA-induced neurotransmitter release. Brain Res. 416: 84-89.